MEMORANDUM

DATE: May 27, 2004

FROM: Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-645

SUBJECT: Action Memo for NDA 21-645, for the use of Myzan (Naproxen/Metoclopramide) Tablets in the acute treatment of migraine

NDA 21-645, for the use of Myzan (Naproxen/Metoclopramide) Tablets in the acute treatment of migraine, was submitted by Pozen, Inc. on 7/31/03. The application contains the results of numerous controlled trials evaluating the effect of this combination treatment on the signs and symptoms of acute migraine, as well as safety data and the requisite pre-clinical, CMC, and clinical pharmacology data. Each component of the combination is an approved compound, and the doses of each proposed in this product (naproxen 500 mg, metoclopramide 16 mg) are below the maximum doses approved for each separately (naproxen, a non-steroidal anti-inflammatory drug, is approved for various arthritides at daily doses up to 1000 mg/day, and metoclopramide, a dopamine receptor antagonist, is approved for use in GERD [among other indications] for a maximum duration of 12 weeks at a maximum daily dose of 45 mg).

The application has been reviewed by Dr. Kevin Prohaska, medical officer (review dated 5/14/04), Dr. Yeh-Fong Chen, statistician (review dated 5/10/04), Dr. Kofi Kumi, Office of Clinical Pharmacology and Biopharmaceutics (review dated 4/26/04), Dr. Tristan Massie, statistician (carcinogenicity; review dated 4/27/04), Dr. Kathleen Haberny, pharmacologist, Dr. Barry Rosloff, pharmacology team leader, Dr. Ni Khin, Division of Scientific Investigations (memo dated 4/6/04), Dr. Josephine M. Jee, chemist (review dated 5/24/04), Kimberly Culley, Division of Medication Errors and Technical Support (DMETS; review dated 4/12/04), Jeanine Best, Division of Surveillance, Research, and Communication Support (review dated 3/16/04), and Dr. Eric Bastings, Acting Neurology Team Leader. The clinical review team recommends that the application not be approved. I will briefly describe the relevant data, and offer the basis for the division's action.

EFFICACY

As noted above, the sponsor has submitted reports of numerous controlled trials examining the effectiveness of Myzan in the acute treatment of migraine. The review team has focused on five of these studies; two of these studies examine the contribution of the individual components of the combination (as required by

the "combination policy" at 21 CFR 300.50), and the remaining three examine the effects of the combination alone compared to placebo (two of these studies also included a sumatriptan 50 mg arm). The two studies that examine the contribution of the components are, in my view, the critical studies in the application, and I will describe the results of these studies below.

Studies 301 and 304

In these studies, patients with an acute migraine headache were randomized to receive a single dose of the combination, naproxen 500 mg, or metoclopramide 16 mg. No placebo group was included in these studies, a design element agreed to with the division. As Dr. Prohaska has described in detail, the analyses that the sponsor presented for these studies differed from the analyses that the sponsor proposed prospectively in the protocols. In addition, the primary assessment of pain relief, a comparison of the proportion of patients who experienced Sustained Pain Relief, defined as having a 0 or 1 pain score at 2 hours after dosing with no increase to a 2 or greater for the next 22 hours, is different from the traditional assessment of the proportion of patients with Pain Relief (0 or 1) at 2 hours after dosing. As Dr. Prohaska notes, with the former outcome measure, a drug may be superior to another while also potentially being worse on the more traditional measure. For this reason, the division has re-thought the appropriateness of this outcome as a primary measure. Nonetheless, we did agree that this primary outcome could be used in these studies.

For the reasons stated, however, I will present the results of the protocol specified analyses for both the protocol specified outcomes and the traditional 2 hour outcomes. Further, I will present the results of the "correct" protocol specified analyses (for Study 304, the sponsor presented an analysis that our statistical consultant recognized as having used an incorrect SAS procedure; she performed the correct analyses, and it is these results I will present).

Study 301

Outcome	**MT100**	**N**	**M**	**M v N**	**M v Met**
N	422	429	213		
Sustained Pain Relief	20.4	19.1	12.7	0.064	<0.001
2 hour pain relief	48.1	46.6	34.3	0.67	<0.001
% Nausea	23.7	26.6	25.4	0.33	0.65
% Photophobia	54.5	52.2	63.4	0.50	0. 03
% Phonophobia	45.7	48.0	52.1	0.50	0.13

Study 304

Outcome	**MT100**	**N**	**M**	**M v N**	**M v Met**
N	1031	1057	528		
Sustained Pain Relief	20.4	17.5	12.9	0.063	<0.001
2 hour pain relief	49.8	46.7	36.6	0.14	<0.001
% Nausea	33.6	36.6	41.5	0.14	0.003
% Photophobia	54.8	53.9	62.1	0.72	0. 007
% Phonophobia	48.0	48.1	52.8	1.00	0.08

Study 306

In this study, patients with an acute migraine headache were randomized to receive one tablet of Myzan, two tablets of Myzan, sumatriptan 50 mg, or placebo. The primary pain outcome was the traditional proportion of patients who achieved Pain Response at 2 hours. The following chart displays the results (with p-values for the comparisons to placebo in parentheses):

Outcome	**MT100**	**2MT**	**Suma**	**Pla**
N	138	142	129	137
2 hour pain relief	52.9 (<.001)	58.5 (<.001)	53.5 (<.001)	29.2
% Nausea	27.5 (.05)	27.5 (.05)	39.5 (.88)	38.7
% Photophobia	47.1 (.002)	45.1 (<.001)	38.8 (<.001)	66.4
% Phonophobia	43.5 (.05)	41.6 (.02)	31.8 (<.001)	55.5

Study 308

In this study, patients with an acute migraine headache were randomized to receive one tablet of Myzan, Sumatriptan 50 mg, or placebo. The primary pain outcome was as in Study 306. In this study, the protocol specified primary

comparison was to be the Myzan vs. sumatriptan comparison. This trial was designed by the sponsor to be a non-inferiority trial, in which their chosen non-inferiority margin was to be 10%. We had informed the sponsor that we would not consider this trial to be able to provide evidence for a comparative claim for Myzan compared to sumatriptan primarily because we believed a "fair" comparison would have included all relevant doses of sumatriptan, and because we could not agree that their choice of a 10% non-inferiority margin was appropriate. Nonetheless, the following chart displays the results of the trial, again, with p-values for the drug-placebo contrasts in parentheses:

Outcome	**MT100**	**Suma**	**P**la
N	332	340	341
2 hour pain relief	44.0 (.001)	47.4 (<.001)	32.0
% Nausea	42.5 (.98)	45.0 (.49)	42.5
% Photophobia	54.8 (.044)	55.9 (.09)	62.8
% Phonophobia	50.9 (.08)	50.9 (.1)	57.8

In addition, because this study was designed primarily to examine the comparison between Myzan and sumatriptan (on 2 Hour Pain Relief), the sponsor calculated the 95% confidence interval for this comparison: this confidence interval was (-4.2, 10.9), with a p-value for the test of equivalence of 0.042. Because this confidence interval does not exclude the 10% margin set prospectively by the sponsor (that is, because the upper bound of the CI is greater than 10%), the test of equivalence has failed (indeed, in order for this to have been considered significant, the p-value for the equivalence test would need to be 0.025 or less; as we can see, this p-value was actually 0.042).

Study 303

In this study, patients with an acute migraine headache were randomized to receive a single dose of Myzan or placebo. Here, patients who failed to respond by 2 hours after dosing were re-randomized to receive either another dose of Myzan or placebo. Drs. Prohaska and Chen have described this study in detail; in brief, by the protocol specified analysis, Myzan was not significantly superior to placebo at 2 hours on Pain Relief (p=0.062), and there were no significant differences on Pain Relief at 2 hours after re-dosing in patients who failed to respond to the first dose (p=.2).

SAFETY

As Dr. Prohaska describes, a total of 2725 patients received at least a single dose of Myzan in Phase 2/3 studies, and 621 and 329 patients completed 6 months and one year of exposure, respectively. In this chronic experience, patients treated on average about 3.2 headaches/month.

Again as Dr. Prohaska describes, there were no unusual or unexpected adverse events seen, and few serious adverse events. He expresses concern, reasonably, that the chronic (intermittent) use of this product might be associated with tardive dyskinesia (TD), a serious and potentially irreversible adverse event well known to occur with chronic exposure to dopamine blocking drugs, and reported in the literature in association with metoclopramide. As he notes, no cases of TD were reported in the database submitted. Two patients were reported to have experienced acute dystonia (another well known complication of dopamine antagonists) and in controlled trials 4% of patients who received 2 tablets of Myzan acutely experienced "Restlessness" compared to <1% of patients in all other treatment groups (1 tablet of Myzan, sumatriptan, naproxen, metoclopramide, or placebo). Although I do not know exactly what is meant by this term, it is possible that this could represent akathesia, another well known and potentially serious adverse event associated with dopamine antagonists (in this regard, the incidence in these trials of "anxiety" was 2% in the 2 tablet Myzan group; again, the highest incidence in any other treatment group was <1%; "anxiety" could also possibly represent akathesia).

Pre-clinical issues

As the review team has noted, the primary pre-clinical issue of concern is the observation that the combination drug was associated with tumor formation in the rat carcinogenicity study.

Specifically, there was an increase in the incidence of benign and malignant tumors in the female and the combined benign and malignant tumors in the male. There was an increase in benign and malignant adrenocortical tumors in the female and in benign adrenocortical tumors in the male animals. Further, there was an increase in benign pheochromocytomas in male rats, and malignant pancreatic islet cell tumors in the males. The sponsor attributes these findings to an increase in prolactin levels (increased prolactin levels were documented in this study), and concludes, on this basis, that they are not relevant to humans.

It is likely that tumor formation with the combination is related to the metoclopramide component (there was not an increase in tumor occurrence in the naproxen-only arm of the study), although, as Dr. Rosloff notes, tumor incidences were greater in the combination arm compared to the metoclopramide alone arm. Whether metoclopramide is genotoxic is unclear; although older studies suggest that it is, more recent studies do not. Again, as noted by Dr.

Rosloff, a p53 mouse study was negative. Although there is a safety margin of about 20-25 with regard to plasma levels (AUC) at which tumors occurred in animals and levels to be achieved in humans at a dose of 16 mg of metoclopramide, it is worth noting that human plasma levels of prolactin are elevated at the doses of metoclopramide patients will receive at the sponsor's proposed dosing regimen.

Other issues

DMETS has found the sponsor's proposed tradename, Myzan, unacceptable because of it similarity to Zyban, which has the potential to result in medication errors.

COMMENTS

The sponsor has submitted the results of at least five controlled trials that purport to demonstrate not only the effectiveness of Myzan as an acute treatment for migraine, but also the contribution of each component to the overall effectiveness. This latter demonstration is required under the regulation governing the approval of fixed combination drug products at 21 CFR 300.50. Of the five studies reviewed by the clinical/statistical review team, only 2, Studies 301 and 304, are capable, by design, of examining the contribution of each component.

In these two studies, the combination consistently was shown to be statistically superior to the metoclopramide component on almost all critical outcomes (pain and the associated symptoms of nausea, photophobia, and phonophobia). The exceptions were the proportion of patients with nausea and phonophobia in Study 301. The absence of a placebo in these two studies raises the question of whether or not the statistically significant differences between the combination and this component are spurious; that is, could the metoclopramide have made patients worse on these outcomes? Although this is theoretically possible, there is no obvious reason to assume this, and, furthermore, at least one other study (Study 306, in which the combination is compared directly to placebo) suggests that the combination is effective against pain and the associated symptoms. These latter data, therefore, together with the combination-metoclopramide comparisons, strongly suggest that the combination-metoclopramide contrasts are not generating spurious outcomes. On the other hand, only in Study 306 are the treatment effects of the combination consistent with those seen in previous studies of acute migraine treatments; the size of the differences between the combination and metoclopramide in Study 304 reached statistical significance undoubtedly only because of the very large sample size studied (see below). In no other single study were there statistically significant between-treatment differences on all four critical outcomes. These outcomes argue for the

conclusion that the sponsor has not provided sufficient evidence (i.e., adequate replication) that the combination is effective.

Even if the effectiveness of the combination is assumed (although again, it has not been shown according to typical standards), the contribution of the metoclopramide component appears not to have been established. The traditional standard for the demonstration of such a contribution would be a statistically significant combination-naproxen comparison on a critical outcome measure. Note that it would not be necessary for there to be significant differences between the combination and any specific component on multiple outcomes in order for the combination policy to be satisfied. That is, if there were reproducibly significant differences between the combination and a given component on a single critical outcome (for example, on pain relief), such an outcome would, in my view, satisfy the requirements of the combination policy (such a finding would clearly document the contribution of the other component to the overall drug effect).

However, in these studies, there is no single outcome measure for which there is a single combination-naproxen comparison that reaches statistical significance according to the traditional standard. As has been seen, the comparisons between combination and naproxen in both studies yield p-values of .062 and .063. Comparisons between the combination and naproxen on the associated symptoms never yield a p-value less than 0.14, with most comparisons yielding p-values of 0.5 or greater.

It must be acknowledged, of course, that p-values of 0.062 are clearly close to the traditional standard of 0.05. Further, it has been argued by some that the requirement for multiple p-values to reach the “traditional” level of .05 in the setting of the multiple comparisons necessitated by the combination policy (in this case, the number of comparisons required are perhaps greater than in the typical case in which the combination policy applies, because there are 4 “primary” outcomes), is too conservative.

Although I am sympathetic to these arguments, it should be noted that the standard we have always applied has been the traditional one; while this is perhaps subject to argument, it is difficult to know how, specifically, to amend this requirement in a given case. One can imagine that the usual requirement, for example, could be suspended if there were a compelling reason to believe that there exists some advantage of the product under review compared to existing approved products for the same indication (although even in such a case, it is not easy to know what the new allowable Type I error should be).

Despite the difficulty of knowing how, quantitatively, to adjust the Type I error in such a case, however, it is worth examining whether or not this is a case in which such an adjustment should be contemplated.

As the review team has noted clearly, the estimate of the contribution of the metoclopramide component derived from these studies, despite the nearly significant differences for the combination-naproxen comparisons, is extremely small. In these two studies, the treatment differences on the Sustained Pain Relief outcome between the combination and the naproxen component varies from about 1-3% (incidentally, it should be noted that the treatment effect of the combination as a whole, on Pain Relief, as estimated by the combination-placebo contrasts in other studies, is much greater, varying from 12-23%). Although we do not have much experience with "typical" effect sizes for the contribution of a specific component to a combination product in the acute treatment of migraine, it should be noted here that the sample sizes in these studies are markedly greater than those typically enrolled in migraine studies; there is no question that the combination-naproxen contrasts yielded p-values as close to 0.05 as they did because of these "inflated" sample sizes. And while it is also true that we do not typically factor into our decisions treatment effect sizes when interpreting statistically significant drug-control differences, it bears repeating that the differences at issue here are not statistically significant.

It is also important to point out that the sponsor has not unequivocally demonstrated the overall effectiveness of the combination. Although Study 306 is one study that can be considered to contribute to a finding of effectiveness, the only other study in which there were consistently significant results on pain and the associated symptoms (this was determined by comparison to metoclopramide, not placebo, and the comparison on the Nausea variable did not actually achieve significance) was Study 304, and, as noted above, these contrasts achieved significance only because of the large sample size; that is, the treatment effects seen were small, and would not have been detected to have been significant in studies of more traditional size.

Despite the extremely small effect of the metoclopramide component (one, again, that does not reach traditional levels of statistical significance), might there be a compelling reason to accept these studies as meeting the requirements of the combination policy, and, therefore, to consider the application approvable?

In my view, there is no such compelling reason.

The sponsor argues that there are patients who cannot be treated with triptans because of the risk of cardiovascular adverse events, and that this product, therefore, provides a reasonable alternative. It is true that triptans are contraindicated in certain patients, but it is also true that a number of over-the-counter medications (anti-inflammatory drugs) are approved for the treatment of acute migraine, and they are not associated with the cardiovascular risks that are (rarely) associated with triptan use.

Further, as the team also notes, chronic use of metoclopramide can be associated with a risk of tardive dyskinesia, a devastating and often irreversible

complication. Although no such cases occurred in the NDA database, this would not be unexpected, given the presumed relative rarity of such an event with intermittent use. As Dr. Prohaska points out, some patients are sure to use the drug more frequently than labeling would suggest, and, in any event, TD might occur even with the intermittent use the sponsor proposes in labeling, but at a rate below that that the chronic use in the NDA could have reliably detected (with about 300 patients exposed for at least one year in the NDA, any event with a true incidence of about 1% or less would not have been reliably detectable).

In addition, as has been described by the review team, the combination (primarily related to the metoclopramide component) causes multiple malignancies in rats. The sponsor asserts that these malignancies are related to increased prolactin levels in animals produced by metoclopramide, and that, therefore, they are irrelevant for humans.

However, as noted by Dr. Rosloff, the sponsor has not adequately documented that the tumor formation is, in fact, the result of increased prolactin levels (although prolactin levels are increased in the animals), and, in addition, and perhaps more important, prolactin levels are increased in humans, and so it is possible that, were increased prolactin the mechanism of tumor formation in animals, this mechanism might also be applicable to human tumor formation. Although the Agency has in the past concluded that animal mammary tumors induced by prolactin-elevating drugs are likely not relevant to humans, this does not imply that other tumor types might not be induced in humans related to increased plasma (in addition, Dr. Rosloff cites an article that suggests that elevated prolactin levels may, in fact, be related to human mammary tumors).

Although there is a margin between levels of metoclopramide demonstrated to be associated with tumors in animals and levels to which humans would be exposed (interestingly, we do not have comparative prolactin levels in animals and humans), there is at least some evidence that metoclopramide may be genotoxic, thereby at least raising the question of whether exposure ratios are relevant (although it should be noted that the more recent genotoxicity studies are negative, as is the p53 mouse study, an assay supposedly sensitive to genotoxic carcinogens).

Taken together, I believe that the data support the conclusion that this product offers no obvious advantage over products currently available for the treatment of acute migraine. Moreover, I believe that the sponsor has failed to unequivocally demonstrate, according to the traditional standard, the contribution of the metoclopramide component to the effect of the drug on any appropriate outcome measure (it is also worth noting that, although the p-values for the combination-naproxen comparison on the primary measure of Sustained Pain Relief approach traditional significance, the p-values for this comparison on the more traditional migraine pain outcome, proportion of patients achieving pain relief at two hours, are 0.14 and 0.67). Further, the near-significant p-values obtained are related to

the extraordinarily large sample sizes employed in these studies, and represent essentially trivial effects of the metoclopramide component. In addition, chronic use of metoclopramide is, and chronic intermittent use as proposed by the sponsor may be (we cannot reliably rule out a rate of less than 1%, given the size of the database), associated with tardive dyskinesia, a devastating, often irreversible complication. Further, animal data suggest that treatment with the combination is associated with multiple malignancies, although I obviously cannot state with any assurance that I know that this represents a significant risk for humans. Finally, the sponsor has not provided definitive evidence that the combination itself is effective. For these reasons, I see no compelling reason to modify the current standard for deciding that a contribution of each component to the effectiveness of the combination has been shown (or even that the combination itself is effective).

Before the application could be approved, I believe that the sponsor would need to submit another well controlled trial, of appropriate size, that unambiguously demonstrates that the combination is effective (clear significant differences between drug and control on all four critical outcomes), and that each component contributes to the overall effect on at least one critical outcome.

For the reasons given above, therefore, I have concluded that the application is Not Approvable. I will issue the attached Not Approvable letter.

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/s/

Russell Katz
5/28/04 01:46:57 PM
MEDICAL OFFICER